# BATHE

## BATH ADDITIVES FOR THE TREATMENT OF CHILDHOOD ECZEMA

Bath Additives for the Treatment of cHildhood Eczema

**Version 4, 2 November 2015**

SPONSOR: University of Southampton

COORDINATING CENTRE: University of Southampton PCPS

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## FUNDER

This trial is primarily funded by the NIHR Health Technology Assessment Programme (ref: 11/153/01) with additional financial support from NIHR Clinical Research Network Service Support Costs .

### Protocol Information

This protocol describes the BATHE trial and provides information about procedures for entering subjects. The protocol should not be used as a guide for the treatment of other subjects; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but sites entering subjects for the first time are advised to contact the Chief Investigator to confirm they have the most recent version.

### Compliance

This trial will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act and all other regulatory requirements, as appropriate.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| AR | Adverse Reaction |
| | |
| CLRN | Comprehensive Local Research Network |
| CRF | Case Report Form |
| CHU 9D | Child Health Utility 9D |
| CTA | Clinical Trial Authorisation |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DFI | Dermatitis Family Impact |
| DMEC | Data Monitoring and Ethics Committee |
| IB | Investigator's Brochure |
| ICH GCP | International Conference on Harmonisation of Good Clinical Practice |
| | |
| IMP | Investigational Medicinal Product |
| IMP | Investigational Medicinal Product |
| MHRA | Medicines and Healthcare products Regulatory Authority |
| NESS | Nottingham Eczema Severity Score |
| NCI | National Cancer Institute |
| PCRN | Primary Care Research Network |
| POEM | Patient-Orientated Eczema Measure |
| REC | Research Ethics Committee |
| SAE | Serious Adverse Event |
| SAR | Serious Adverse Reaction |
| SmPC | Summary of Product Characteristics |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| UAR | Unexpected Adverse Reaction |
| UoSCTU | University of Southampton Clinical Trials Unit |
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## KEYWORDS

Eczema; atopic dermatitis; child; emollients; baths; randomised controlled trial; primary care

## TRIAL SYNOPSIS

| | |
|---|---|
| **Title** | Bath Additives for the Treatment of cHildhood Eczema |
| **Acronym** | BATHE |
| **Chief Investigator** | Dr Miriam Santer |
| **Objectives** | To determine the clinical and cost-effectiveness of adding bath emollient to the standard management of atopic eczema in children |
| **Trial Configuration** | Pragmatic 2-armed non-blinded randomised controlled trial |
| **Setting** | GP practices in England and Wales |
| **Target Population** | Children aged >1 and <12 years with atopic eczema. We will exclude children with inactive or very mild eczema (5 or less on Nottingham Eczema Severity Scale). We will exclude children who usually have a bath less than once per week. |
| **Number of participants** | 423 |
| **Interventions** | Bath emollients along with standard eczema care. Children will be randomised online to either regular bath emollients prescribed by the GP in addition to standard eczema care, or to standard eczema care without bath emollients. Both groups will be given general advice regarding eczema care in line with NICE guidance. |
| **Duration of study** | Study set-up starts on 1 May 2014 for 42 months:<br>1 November 2014 to 31 July 2015 internal pilot recruitment phase<br>1 August 2015 to 30 April 2016 main recruitment phase<br>1 May 2016 to 30 April 2017 participants complete 12 month follow-up<br>1 May 2017 to 31 October 2017 data preparation, analysis, final reports<br><br>Follow up for each participant will be 12 months. |
| **Randomisation** | Online randomisation will be used.<br>It will not be possible to carry out a blinded study as it would not be possible to create a convincing placebo for bath emollients, which make the bath 'greasy'. |

| | |
|---|---|
| **Outcome measures** | Primary outcome:<br><br>We will measure weekly difference in eczema severity between groups by administering POEM (Patient-Oriented Eczema Measure) questionnaires weekly for 16 weeks.<br><br>Secondary outcomes:<br><br>1. Number of eczema exacerbations resulting in a primary healthcare consultation over 1 year. This will be assessed by a review of participants' primary care records at 1 year, and exacerbations will be defined as consultations where there is mention of eczema and topical steroid or topical calcineurin inhibitor has been advised or prescribed.<br><br>2. Eczema severity over 1 year by administering POEM every 4 weeks from 16 weeks to 12 months.<br><br>3. Disease-specific QoL at baseline, 16 weeks and 1 year, measured by DFI (Dermatitis Family Impact),.<br><br>4. Generic QoL as measured by the Child Health Utility 9D (CHU 9D), a paediatric health related quality of life measure for use in economic evaluations.<br><br>5. Type (strength) and quantity of topical steroid/calcineurin inhibitors prescribed, measured by GP record review at 12 months. |
| **Statistical methods** | SAMPLE SIZE: The sample size was calculated for repeated measures ANOVA in weekly POEM scores over the 16 week observation period. Using data from a similar population in the SWET trial we aim to detect a mean difference of 2.0 (sd 7.0) between intervention and control groups. An alpha of 0.05 and power 0.9 gives a sample size of 338. Allowing for 20% loss to follow-up this gives a total sample size 423, i.e. 141 for each of the three participating regions. As only 80% of participants are strictly adherent to treatment allocation and we would like to report a per protocol analysis in addition to an intention to treat analysis, our total target is 491.<br><br>ANALYSIS: We will use repeated measures ANOVA to analyse weekly POEM scores or a mixed model to allow for missing data. We will compare differences between groups in number of exacerbations using linear regression methods. We will control for possible confounders, such as baseline eczema severity and child's age. Analyses will be carried out on an intention to treat basis. |
| **Health economic analysis** | The within trial economic analysis, adherent to guidelines for good economic evaluation practice, will include the primary economic evaluation which will be in the form of cost-effectiveness analysis (CEA), and a secondary economic evaluation in the form of cost-utility analysis (CUA). As part of the study, resource use data in primary and secondary care associated with eczema will be collected. The main viewpoint of the study will be that of the NHS. However, other resource use data will be collected to allow for a secondary analysis from a societal perspective. All cost-effectiveness results will be presented on the cost-effectiveness plane and cost-effectiveness acceptability curves. |

## SCHEDULE OF OBSERVATIONS

| **Outcomes collected** | Screening | 0 weeks<br>Baseline | Weekly for<br>15 weeks | 16 weeks | 4 weekly for 32 weeks | 52 weeks |
|---|---|---|---|---|---|---|
| **Data collection time points** | | 1 | 15 | 1 | 8 | 1 |
| **Location** | Post or phone | Clinic or home | Post or online | Post or online | Post or online | Post or online |
| Eligibility checks | ✓ | | | | | |
| Eczema severity (NESS) | ✓ | | | | | |
| Demographics | | ✓ | | | | |
| Prior belief in bath emollients | ✓ | ✓ | | | | |
| Service use (carer report) | | ✓ | | ✓ | ✓ | ✓ |
| Medication use (carer report) | | ✓ | | ✓ | | ✓ |
| POEM | | ✓ | ✓ | ✓ | ✓ | ✓ |
| DFI | | ✓ | | ✓ | | ✓ |
| | | | | | | |
| CHU-9D | | ✓ | | ✓ | | ✓ |
| Questions about washing | | ✓ | | ✓ | | ✓ |
| Adverse effects from bathing (both groups) | | | ✓ | ✓ | ✓ | ✓ |
| Adherence to/avoidance of bath emollients (both groups) | ✓ | | | ✓ | | ✓ |
| Eczema consultations (notes review of 12 months before and after recruitment date) | | | | | | ✓ |
| Eczema referrals (notes review of 12 months before and after recruitment date) | | | | | | ✓ |
| Medication use (notes review of 12 months before and after recruitment date) | | | | | | ✓ |

## LAY SUMMARY

Eczema is a skin condition that is very common in young children. It causes itching and sleep problems which lead to distress for the child and the rest of the family and can also impact on schooling and everyday tasks. The main treatments are emollients which moisturise the skin, and steroid creams/ointments to treat flare-ups caused by skin inflammation. A NICE guideline on childhood eczema has recommended 'complete emollient therapy' – a care package that includes directly applied emollient, soap substitute emollient and bath emollient (a liquid added to the bath). However, the guideline highlighted that there is little research evidence on whether adding in a bath emollient is helpful.

While health professionals agree about the benefits of directly applied emollients and avoiding soap for children with eczema, there is less confidence in the possible additional benefits of bath emollients. It is possible that they do help because they are easy to pour in the bath and it is likely that they come into contact with all of the skin. But it is also possible that the emollient effect is much less than the direct application of emollients onto the skin, and not enough to produce any benefit. Bath emollients can have adverse effects as they sometimes cause stinging and redness of the skin, potentially cause accidents through leaving the bath slippery and may rot bath mats and lead to increased time spent cleaning the bath. Furthermore, there is concern that some families view bath emollients as an alternative to directly applied emollients and are therefore using a less effective therapy instead of something that would help their child's eczema more. Bath emollients cost the NHS over £16 million per year, a substantial sum given the lack of evidence for their benefit.

This trial will measure whether bath emollients help children with eczema. Children aged 1 to 11 will be randomly allocated to 2 groups: (1) standard eczema management with bath emollient and (2) standard eczema management without bath emollient. We will ask parents or carers to complete weekly diaries including a short questionnaire about eczema severity for the first 4 months, the time period during which the greatest effect is likely, and will check how many flare-ups of eczema are recorded in their GP records over 1 year. We will also ask parents and carers about any side effects or difficulties they have using the treatment (adherence to treatment). We will also measure use of additional treatments, such as directly applied emollients, from GP prescribing. Previous work suggests that few families buy these products over the counter as they are available free on prescription for children.

The British National Formulary lists 13 different bath emollients, but in practice a few of these are commonly prescribed. For this reason we will encourage participating practices to issue Oilatum, Balneum or Aveeno bath emollients, which are the most frequently prescribed bath emollients in the UK and appear in local prescribing formularies for participating centres. The cost of the study reflects the organisation required to collect high quality data for over 400 children over a 1 year time period, the training of nurses for recruiting participants into the trial and the employment of staff to run the trial, including specialists in trial management, statistics, health economics, dermatology, primary care, and patient and participant representation. NHS costs include time spent by practice staff in carrying out recruitment and notes review, as well as the costs of bath emollient prescribing within the study.

The majority of children with eczema are managed in primary care and this study will therefore identify participants through a number of different general practices, both by practices posting invitations to eligible families and also by GPs and health visitors inviting eligible families during routine clinics. The combined expertise within this team covers extensive experience in successfully carrying out dermatology trials and also in carrying out large pragmatic trials in primary care.

# 1. BACKGROUND AND RATIONALE

Childhood eczema is very common, affecting over 20% of children aged 5 or under at some point (Williams et al 2008). It can cause significant distress to affected children and their families due to sleep disturbance and itch (Lewis-Jones and Finlay 1995, Chamlin et al 2004). Research from secondary care suggests that the impact on quality of life in eczema is second only to cerebral palsy, with greater impact reported than for asthma or diabetes (Beattie and Lewis-Jones 2006, Kemp 2003).

Skin complaints are the second most common reason for GP consultation in children under the age of five (RCGP 1995). Health and societal costs of eczema care are difficult to estimate as they vary widely by population under study, but eczema is thought to cause a similar economic burden to that for asthma (Herd et al 1996, Verboom et al 2002).

Emollients form the mainstay of treatment for eczema and should be used regularly by all patients, whether experiencing mild, moderate or severe disease. Other treatments, such as topical corticosteroids, should be used in addition where necessary (NICE Guideline on Atopic Eczema in Children 2007).

Emollients are thought to act by providing a protective layer over the skin, decreasing moisture loss and occluding against irritants. There are three methods of application of emollients:

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|---|---|
| Leave-on emollients (directly applied emollients) | Where emollients are applied to the skin and left to soak in. |
| Soap substitutes | Where emollients are used instead of soap or other washing products |
| Bath emollients (or bath additives) | Oil and/or emulsifiers disperse in the bath. |

Adapted from NICE Guideline on Atopic Eczema in Children (2007)

The NICE Guideline on Atopic Eczema in Children found no studies that evaluated the effectiveness of emollients in children with atopic eczema. The available data consisted of isolated case series and case reports, with no controlled studies comparing emollients to placebo/no active intervention. Irritant adverse skin reactions such as stinging were documented to occur with bath additives.

The Guideline Development Group recommended that healthcare professionals should offer children with atopic eczema a choice of unperfumed emollients to use every day for moisturising, washing and bathing and that this could include a combination of products or one product for all purposes. The Group also recommended further research into the most effective and cost-effective combinations of emollient products to use for the treatment of childhood atopic eczema.

A systematic review has revealed no convincing evidence for the use of bath emollients in the treatment of eczema (Drug & Therapeutics Bulletin 2007, Tarr & Iheanacho 2009), yet they are widely prescribed at a cost of over £16m per year to the NHS (Drug & Therapeutics Bulletin 2007) and represent 38% of the total costs of eczema treatments prescribed to preschool children (Emerson et al 2001). Updated searches show no substantial trials since 2007 (The Global Resource of Eczema Trials 2014). There is widespread clinical consensus on the need for leave-on emollients and soap substitutes, but less certainty regarding the benefits of bath emollients.

Potential harms from using bath emollients include skin irritation and greasier baths, leading to increased rotting of bath mats, increased use of cleaning products and increased risk of slips and accidents. There is also a concern that people who use bath emollients in place of leave-on emollients are receiving substandard emollient therapy (Tarr and Iheanacho 2009).

A Research Priority Setting Partnership exercise for eczema was conducted by the James Lind Alliance and published in 2012. The exercise identified priorities for eczema research, including, 'Which is the best way for people with eczema to wash'? (Batchelor et al 2013)

# 2. TRIAL OBJECTIVES

To determine the clinical and cost-effectiveness of bath emollient treatment, in addition to standard clinical care, for childhood eczema in primary care.

# 3. TRIAL DESIGN

It will not be possible to carry out a blinded study as it would not be possible to create a convincing placebo for bath emollients, which make the bath feel 'greasy'. Our primary outcome is participant-reported, as our main concern is with the impact of symptoms rather than eczema appearance (objective assessment). Ideally, we would also include an objective assessment of eczema severity carried out by a blinded assessor. However, this would increase costs significantly as we would then need two members of the research team to visit practices; one to carry out the consent, randomisation, arrange for a prescription if necessary and another to carry out the assessments. As our primary outcome is participant-reported, and therefore unblinded, incurring substantial additional costs for an objective secondary outcome does not seem warranted.

An internal pilot RCT will be conducted over the first nine months of trial recruitment due to: (1) uncertain prevalence of different eczema severities in primary care; (2) uncertain feasibility of collecting weekly POEM scores in this population and; (3) uncertainties around recruitment and retention. Recruitment, retention and completeness of weekly data collection will be monitored monthly by the Trial Management Group. If progress is below target, strategies will be implemented to remedy this. We have pre-specified the following progression criteria to be assessed by the Trial Steering Committee at nine months (target recruitment = 150 participants by 9 months of recruitment).

| **Criteria to be assessed at 9 months** | **Proposed action** |
|---|---|
| 80% of target recruitment | Continue with main trial as planned |
| 50 – 80% of target recruitment and retention | Trial Steering Committee discuss problems with the Trial Management Group and urgently implement remedies |
| Less than 50% of target recruitment and retention | Discuss plans with Trial Steering Committee and NIHR HTA. Consider stopping trial. |

## 3.1 TRIAL OUTCOME MEASURES

**Primary outcome measure**

POEM (Patient-Oriented Eczema Measure) is a patient reported outcome based on symptoms over the previous week which can be completed by the child's carer (Charman et al 2004). POEM is the only patient reported outcome that demonstrated sufficient validity and repeatability in a systematic review of outcome measures for eczema (Schmitt et al 2007). Our

primary outcome measure is based on repeated measures of POEM data collected weekly over 16 weeks because this reflects the impact of this relapsing and remitting chronic condition better than comparing outcomes at a single follow-up point.

Because of the burden of weekly data collection on participants we have limited weekly data collection to the first 16 weeks of the trial. Participants may choose to complete this either online or by post. If we receive no data after 16 weeks we will telephone to seek core data by phone.

**Secondary outcome measures – notes review**

Number of eczema exacerbations resulting in a primary healthcare consultation over 1 year will be measured by GP record review. Exacerbations will be defined as consultations where there is mention of eczema and topical steroid or topical calcineurin inhibitor has been advised or prescribed. (Records to be examined by member of practice team or, if unable to do so, member of research team).

Number of GP appointments and dermatology referrals and prescribing for eczema will be assessed by GP record review. (Records to be examined by member of practice team or, if unable to do so, member of research team).

**Secondary outcome measures - Carer reports**

POEM (Patient-Oriented Eczema Measure) change at 12 months.

Use of bath emollient will be asked at baseline, 16 weeks and 52 weeks in both groups to assess adherence to treatment allocation. We will ask both groups at baseline to be open about use of bath emollients and other bath products, giving carers 'permission' to say if they have not been adhering to treatment allocation, in order to measure contamination. (Carer report online or by post)

Adverse effects of bathing, such as stinging in the bath or slipping in the bath or bathroom will be asked weekly for the first 16 weeks then monthly in both groups to allow exploration of any differences between groups. (Carer report online or by post)

Use of leave-on emollients, topical steroids and topical calcineurin inhibitors will be monitored by carer report. (Carer report online or by post)

Service use (GP, Pharmacy, Walk-in centres, NHS direct) will be monitored by carer report using the CSRI (Client Service Receipt Inventory). (Carer report online or by post)

We will measure expectation of benefit of bath emollients at baselineto be able to explore how much any effects seen might be due to expectation.

Disease-specific QoL, measured by DFI. DFI (Dermatitis Family Impact) (Lawson et al 1998) is a widely-used validated instrument measuring impact of eczema on the family's quality of life. (Carer report online or by post)

The use of EQ-5D in children has been questioned and it does not capture QoL issues pertinent to childhood eczema, mainly sleep disturbance and child's mood. The CHU 9D (Child Health Utility 9D) (Stevens 2011) is a paediatric generic preference-based utility measure exclusively developed with children aged 7-11 years and is more suitable for capturing quality of life impact related to atopic eczema. Personal communication with the team who developed this measure confirmed that studies are underway trialling its application in children age 5-7 years but, to our knowledge, there are no studies reporting for infants. There are no suitable utility measures validated for very young children age 1-4 years but the CHU-9D performed well in the SPaCE trial (data currently being prepared for publication).

### 3.2 EVALUATION OF TRIAL PROCESSES

We will carry out interviews with 20 parents/carers in order to investigate participants' experiences of taking part in the trial, for instance perceived barriers and facilitators to recruitment, adhering to study allocation group and completing study materials (in particular, weekly questionnaires). Interviews will be carried out either in participants' homes or by phone, depending on parent/carer preference. Parents/carers will be asked at their baseline appointment if they would be interested in taking part in such an interview. If they express interest then they would be given further information to consider before being phoned to ask whether they are happy to participate. They would then be asked to complete a consent form specific to the interview prior to it commencing.

## 4. SELECTION AND ENROLMENT OF PARTICIPANTS

### 4.1 INVITATION TO PARTICIPATE

Parents /legal representatives will be invited through mail out and opportunistic recruitment by participating practices. Invitations will be sent to the parent or legal representative of any child aged >1 and <12 years who has a recorded diagnosis of eczema (Read codes: Eczema NOS; Atopic eczema/dermatitis; infantile eczema) and who has obtained one or more prescriptions for drugs acting on the skin (BNF chapter 13) over the previous 12 months, as a recent prescription would suggest that the eczema is still active.

Parents /legal representatives will be sent an invitation letter on GP-headed notepaper, participant information sheet (PIS), a brief screening questionnaire and a reply slip to return to the study team. The brief screening questionnaire will include a copy of the Nottingham Eczema Severity Score (NESS) (3 questions)and other questions to check that they meet UK diagnostic criteria for eczema (Williams et al 1994), in order not to waste carers' time with making recruitment appointments if their child would not be eligible for the study. They will be offered the option to respond to these online instead of postally.. The study team will then contact them to discuss the study further and to confirm eligibility criteria, before inviting them to a recruitment appointment with the Research Nurse/Clinical Studies Officer at their GP practice (or at participant's home if no room is available at GP practice). If the child is not eligible for the study we will write to thank them for their interest and include a brief information leaflet about eczema.

Participants may also be recruited opportunistically during a consultation. In which case, the GP will provide the carer with an invitation letter directly along with the enclosures listed above – PIS, reply slip, NESS and pre-paid envelope for directly responding to the study team.

Previous experience from pilot SPaCE trial (Santer et al 2014) suggests that we will obtain approximately 7 participants from each general practice, which means 58 practices will be needed to support the study, approximately 19 from each of the 3 recruiting centres (in order to recruit 135 participants from each centre). We currently have more than 250 practices in our primary care networks and do not anticipate any problems in getting sufficient numbers of practices to take part.

### 4.2 INCLUSION CRITERIA

Children (aged between >1 year and <12 years) with mild to severe eczema as defined by the UK Diagnostic Criteria for Atopic Eczema (Williams et al 1994) and with eczema severity at entry judged using the Nottingham Eczema Severity Scale (NESS) (Emerson et al 2000).

Children will only be recruited if their carers accept that there is uncertainty about the value of bath emollients (equipoise) and they are prepared for their child to be randomised to either group.

### 4.3 EXCLUSION CRITERIA

Exclusion criteria include: very mild eczema (NESS score 5 or less) (to avoid floor effects); child not using a bath at least once a week; carer (or child) not willing for child to be randomised to either bath emollient or no bath emollient; inability to give informed consent or insufficient English to complete outcome measures. If a family has more than one child who meets the eligibility criteria, then they will be asked to choose just one child to participate in the trial.

Children taking part in other clinical trials will be excluded.

### 4.4 REGISTRATION/RANDOMISATION PROCEDURES

If a parent or legal representative who has received the invitation letter is willing to take part then they will reply directly to the research team giving them their contact details. A member of the research team will contact them to (1) answer questions; (2) confirm eligibility criteria; and (3) arrange an appointment with the Research Nurse/Clinical Studies Officer at their practice (it is not essential that the child attends this as it will be the carer who will complete all the measures.)

At the baseline appointment, all eligibility criteria will be confirmed and the Research Nurse/Clinical Studies Officer will answer any further questions and seek informed consent. The parent or legal representative will be asked to login to the computer with the details that the Research Nurse/Clinical Studies Officer will give them. They will then need to change their password prior to completing baseline questionnaires and online randomisation. The parent or legal representative will need to share the result of the randomisation with the Research Nurse/Clinical Studies Officer so that she can arrange for a prescription for bath emollient for those randomised to that arm. This will be entered as a repeat prescription so further supplies may be obtained if necessary. The Research Nurse/Clinical Studies Officer will also ask the GP to annotate the patient's GP record to remind the GP not to prescribe bath emollient for that patient for the 12 months they are in the study but if they need to then they will inform the study team.

### 4.5 WITHDRAWALS

Any participants who choose to withdraw from the study will be asked to complete an end of study questionnaire. The number of participants who withdraw from the study with the reasons for withdrawal will be summarised by randomised treatment allocation.

# 5. TREATMENTS

## 5.1 TREATMENT ARMS

**1. Standard care alone**

'Standard care' in this study constitutes usual GP care, supplemented by evidence based guidance. We will provide basic information on eczema care at baseline to GPs in both groups in the form of a booklet based on NICE guidance (2007). We will provide both groups of participants with basic information about eczema and how to wash children with eczema, based on Patient Information Leaflets from the Nottingham Support Group for Carers of Children with Eczema.

Other than providing evidence based guidance we will not aim to influence how GPs manage eczema in the Standard care group, except that we will seek to highlight in participants' electronic record that they have been allocated to standard care alone and should therefore not be prescribed bath emollient for the duration of the study.

Standard care of eczema in the UK is generally a series of ad hoc 10 minute consultations in primary care initiated by parents / carers when they deem it necessary. GPs refer to specialist services when they feel this to be necessary.

We will encourage adherence to treatment allocation by ensuring that participating general practices are committed to supporting the study and receive clear advice regarding maintaining treatment allocation, including the use of computer alerts (where possible) to ensure that they do not inadvertently prescribe bath emollients to those randomised not to use them.
Parents / carers of participants in both groups will have a baseline appointment to discuss the trial, complete informed consent, complete baseline questionnaires and undergo randomisation. The clinical studies officer / nurse will discuss how to wash children with eczema at this appointment with parents / carers from both groups in order to minimise differences in washing practices between groups. Many people use bath emollients as soap substitutes and it is likely that some of the participants in this trial will already be doing so. We will ask all participants to either wash with water alone or to use a leave-on emollient as a soap substitute and back this up with written advice.

**2. Standard care plus prescription of bath emollients**

GPs will receive information about evidence-based eczema management and participants will receive basic information about eczema and how to wash children with eczema, as above. For those allocated to receive bath emollients, the Research Nurse/Clinical Studies Officer will obtain a prescription for bath emollients from a GP in the participating practice and will ask the prescriber to enter this as a 'repeat' prescription so that carers may obtain further supplies as necessary, reflecting usual prescribing in primary care. Carers will be asked to use bath emollients as prescribed or described on the packaging, to reflect how they are used in usual practice.
The British National Formulary (BNF) lists 13 different bath additives, but in clinical practice a few of these are commonly prescribed. For this reason we will encourage participating practices to issue Oilatum, Balneum or Aveeno bath emollients, which account for the majority of bath emollient prescriptions issued in the UK and appear in local prescribing formularies for participating centres.

Participants in the intervention group who have previous experience of bath emollient can choose from Oilatum, Balneum or Aveeno, otherwise the order they are offered in will be determined locally. If they wish to change bath emollient during the trial then

they will be encouraged to use one of these, but may choose others if their GP is happy to prescribe them. Some emollient products contain additional ingredients such as antipruritics and antiseptics (for instance, Dermol) and we would ask participants not to use these.

### 5.2 RETENTION

We will encourage continued engagement for participants in both groups by giving a £10 gift voucher at baseline appointment to thank them for their time, sending trial newsletters with updates on progress, cards and small gifts at key milestones (such as colouring set or other age-appropriate item for child) and highlighting that participants completing their final questionnaire will be entered into a prize draw to receive a tablet device.

No further face-to-face contact is planned after the initial baseline recruitment appointment. If parents / carers in either group do not complete outcome measures then they will receive reminders by email or phone from the study team.

## 6. PHARMACOVIGILANCE

### 6.1 BACKGROUND

This is a Type A CTIMP, i.e. the risk of the medicinal product is not higher than the risk of standard medical care. The products under investigation have been used widely for many years and are available over the counter without a prescription. Oilatum Fragrance Free Junior and Balneum bath oil are licensed for use in the EU and are being used within their licensed indication in this study. Aveeno Bath Oil does not have a EU pharmaceutical Marketing Authorisation but is approved by the ACBS (Advisory Committee on Borderline Substances) for the treatment of eczema and has been widely prescribed and purchased over the counter for many years with no safety concerns. When a participant is randomised to the intervention the Research Nurse/Clinical Studies Officer will arrange for this to be prescribed and recorded by their own GP. It will therefore be labelled by the community pharmacist in the usual way and products will be issued with information leaflets listing indications, contra-indications, possible adverse events, etc., in the usual way. This is not a blinded trial.

Known adverse reactions to bath emollients (BE) are recorded in the Summary of Product Characteristics for Oilatum Fragrance Free Junior and Balneum bath oil. These include: skin irritation, rash, erythema (redness), pruritus (itch.) Accidental ingestion may cause gastrointestinal irritation with nausea, vomiting and diarrhoea. There is an increased risk of slipping due to the oil film on the skin and the oil film in the bath or shower.

### 6.2 DEFINITIONS

The Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, provides the following definitions relating to adverse events in trials with an investigational medicinal product:

**Adverse Event (AE):** any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

*An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.*

**Adverse Reaction (AR):** all untoward and unintended responses to an IMP related to any dose administered.
*All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.*

**Unexpected Adverse Reaction (UAR):** an AR, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure (IB) for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product*).*
*When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the IB/SmPC which occur in a more severe form than anticipated are also considered to be unexpected.*

**Serious Adverse Event (SAE)** or **Serious Adverse Reaction (SAR):** any untoward medical occurrence or effect that at any dose:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

**Suspected Unexpected Serious Adverse Reaction (SUSAR):** any suspected adverse reaction related to an IMP that is both unexpected and serious.

## 6.2 CAUSALITY

We expect that most adverse events that occur in this trial will be expected treatment-related adverse reactions as listed in the SmPCs for bath emollients, such as skin irritation or slipping in the bath. The assignment of the causality should be made by the principal investigator using the definitions in the table below.

If any doubt about the causality exists the local investigator should inform the trial manager who will notify the Chief Investigator. Other clinicians may be asked for advice in these cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA will be informed of both points of view.

| Relationship | Description |
|---|---|
| **Unrelated** | There is no evidence of any causal relationship |
| **Unlikely** | There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the bath emollient). There is another reasonable explanation for the event. |
| **Possible** | There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the bath emollient). However, the influence of other factors may have contributed to the event. |
| **Probable** | There is evidence to suggest a causal relationship and the influence of other factors is unlikely. |
| **Definitely** | There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. |

## 6.3 REPORTING PROCEDURES

The investigational medicinal products under investigation in this trial are widely used and a significant amount of safety data exists. Serious adverse events related to the use of the bath emollients in this trial are therefore not expected. It is possible, however, that new and unexpected adverse reactions might come to light. Therefore the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the trial manager in the first instance.

### 6.3.1 Adverse Reactions

Information about *expected* adverse reactions to the investigational medicinal product which are listed in the Summary of Product Characteristics (i.e. pruritus, reddening, itching, skin irritation, rash, accidental ingestion, slipping) will be collected in trial questionnaires (or the withdrawal form, where applicable) and therefore need not be reported as an adverse event.
Any *unexpected* adverse event which could reasonably have been caused by use of the IMP should be reported on the SAE form under the category "Other" and sent to the sponsor's representative (Trial Manager) within 24 hours of the site becoming aware of the event.

### 6.3.2 Non-serious Adverse Reactions

Non-serious medical occurrences which cannot be causally related to trial participation need not be reported, as this would represent a significant burden of unnecessary data collection in this age group.

### 6.3.3 Serious Adverse Events and Reactions

SAEs and SUSARs should be reported within 24 hours of the local site becoming aware of the event.

For the purposes of this study, a serious event is one which:

(a) results in death,
(b) is life-threatening,
(c) requires hospitalisation or prolongation of existing hospitalisation,
(d) results in persistent or significant disability or incapacity, or

(e) Other - an adverse reaction the nature or severity of which is not consistent with the known information about the drug as provided in the Summary of Product Characteristics.

Hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

**Reporting Details**
An SAE/SUSAR form should be completed for all SAEs and SUSARS and faxed to the trial manager within 24 hours:

Complete the SAE/SUSAR form with as many details as possible and fax it to the trial manager together with anonymised relevant treatment forms and investigation reports.
**Or**
Contact the trial manager by phone for advice and then fax or email a scanned copy of the completed SAE/SUSAR form.

The SAE/SUSAR form asks for: nature of event, date of onset, outcome and causality (ie, unrelated, unlikely, possible, probably, definitely). The GP lead at the site should assign the causality and expectedness of the event with reference to the current IMP Summary of Product Characteristics. Additional information should be provided as soon as possible if the event/reaction has not resolved at the time of reporting.

The sponsor will notify the MHRA and Ethics Committee of all SUSARs occurring during the trial (within 7 days for fatal or life-threatening SUSARs and 15 days for all others). All investigators will be informed of all SUSARs occurring throughout the trial.

### 6.3.4 Follow Up and Post-study SAEs

The reporting requirement for SAEs affecting subjects applies for all events occurring up to 24 hours after the last use of bath emollients. All unresolved adverse events should be followed by the investigator until resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's general practitioner, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study.

# 7. ASSESSMENT AND FOLLOW-UP OF SUBJECTS

## 7.1 DEFINITION OF END OF TRIAL

For the purpose of regulatory and ethical requirements, the end of the trial is defined as the date of the last data capture for the last participant undergoing protocol treatment. Trial recruitment will end when 423 participants have been randomised, or at the request of the Trial Steering Committee.

# 8. STATISTICS AND DATA ANALYSIS

Data and all appropriate documentation will be stored for 10 years after the completion of the trial, in line with University of Southampton policy.

## 8.1 SAMPLE SIZE

The sample size was calculated for repeated measures ANOVA in weekly POEM scores over the 16 week observation period. Using weekly data from a similar population in the SWET trial (10) we aim to detect a mean difference of 2.0 (sd 7.0) between intervention and control groups. A difference of 2.0 in POEM scores is regarded as small (10) and differences smaller than this are very unlikely to be clinically important for such a common condition. We wish to be able to detect this small difference as the intervention is relatively inexpensive and even small effect sizes are likely to be cost-effective. An alpha of 0.05 and power 0.9 gives a sample size of 338. Allowing for 20% loss to follow-up this gives a total sample size of 423.

We would like to report a per protocol analysis in addition to an intention to treat analysis and early data suggest that approximately 80% of participants in both groups are strictly adherent to treatment allocation. If only 80% of participants are adherent to treatment allocation, then we have data we can use on 270 people. To get back up to 90% power for this group, we would need another 338-270= 68 participants, giving a target recruitment of 491.

## 8.2 STATISTICAL ANALYSIS

We will use repeated measures analysis of covariance (ANCOVA) to explore whether there is a significant difference between mean POEM scores over the 16 week period in the intervention and standard care groups. The analysis will control for possible confounding effects of key covariates, such as baseline eczema severity and age of child, and will explore any interactions with the use of other bath additives and the use of other medications. However, because ANCOVA relies on analysis of complete cases only, the levels of missing data will be reviewed and, if appropriate, the data will be analysed using mixed models instead, which allows incomplete cases to contribute to the analysis.

Primary analyses will be carried out on an intention to treat basis. We will carry out a per protocol analysis in addition to this as monitoring reveals a substantial proportion are not following their treatment allocation (i.e. intervention group stop using bath emollient or control group start bath emollient).

The statistician carrying out the analysis will be blind to allocation group.

## 8.3 ECONOMIC ANALYSIS

Evaluation will be conducted from the NHS perspective. The principal costs are those associated with the use of bath emollient and the primary and secondary health care contacts and medication. We will collect patient level data from routine sources, including practice records. We will collect private family borne costs linked mainly to exacerbations at the pilot phase; if these costs prove to be important then we will collect these data during the main study using a carer/parent completed questionnaire based on the CSRI (Client Service Receipt Inventory) (Beecham & Knapp 2001) and adjusted to capture expenditure in atopic eczema. Health care resources will be valued using published national sources and the British National Formulary.

There will be two components to the economic analysis, and costs will be related both to the primary and secondary outcomes: (i) the cost per unit change as measured by the primary outcome (POEM) at 16 weeks; (ii) every effort will be made to report cost per exacerbations avoided (subjective measure), however should defining exacerbations prove to be unreliable the cost per unit score change of the disease-specific QoL measure at 1 year will be reported; and (iii) the cost per QALY gain at 1 year. The outcome measure (POEM) used to assess cost-effectiveness are validated tools recommended in NICE guidance (2007).. The 16 week POEM scores for severity will allow us to report costs by severity levels. Cost-effectiveness will also be reported by severity at 16 weeks, as assessed at baseline, if it proves to be different. There are no recommended generic preference-based quality of life measures to estimate QALYs for children with atopic eczema and we will therefore calculate QALYs based on CHU-9D as we feel this to be the most appropriate measure to assess generic QoL in this trial. Therefore, special consideration will be given to the methods of obtaining utility values and estimating QALYs for very young children, and every effort will be made to obtain robust utility values. The evaluation will include plotting cost-effectiveness acceptability curves generated from bootstrap analysis (Black 1990).

Sensitivity analysis will explore the impact of differences in key costs and outcome assumptions; including assessing appropriateness of QALY estimations for very young children. If private family-borne costs are an important burden for parents then these costs will be included and the results will be presented in the form of sensitivity/scenario analysis. Due to the time frame of the follow up period (1 year) discounting is not required.

# 9. REGULATORY ISSUES

## 9.1 CLINICAL TRIAL AUTHORISATION

This trial has a Clinical Trial Authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA).

## 9.2 ETHICS APPROVAL

Full ethical approval has been obtained through the National Research Ethics Service (NRES) from Newcastle and North Tyneside 1 Committee, reference 14/NE/0098.

Possible adverse effects from bath emollients include skin irritation and the risk of accidents through causing slippery baths and rotting bath mats. Carers will be warned of these side effects on entering the trial.

Children up to the age of 12 years will be eligible for enrolment in the trial. Age-appropriate Patient Information Leaflets (PILs) will be available for children, in addition to PILs for carers. These PILs will contain information about the trial, how the trial might affect the child / family, and outline the likely benefits and risks. Assent forms are available for recording assent of older children, if this is judged to be appropriate by their parent/legal guardian and Clinical Studies Officer/Research Nurse at the recruiting appointment. This would be in addition to the consent form (from parent / legal guardian) which will be a requirement for study entry.

Details of the trial will also be available via a dedicated trial website, and enquiries will be directed via the trial co-ordinating centre. For children of school age, efforts will be

made to arrange appointments outside of school hours whenever possible or, if carers prefer, then they may have the appointment without the child present.

**9.3 CONSENT**

A parent or legal representative of the minor being invited to take part in the trial will give informed consent prior to agreeing to participate.

This will be done in the GP surgery at the initial screening visit with the Research Nurse/Clinical Studies Officer. Randomisation and baseline data collection will be carried out online but paper versions of all documents will be available in case there are issues around participant log-in or accessibility to an internet connection.

**9.4 CONFIDENTIALITY**

Subjects' identification data will be required for the registration process. The University of Southampton will preserve the confidentiality of subjects taking part in the trial.

**9.5 INDEMNITY**

The sponsorship and indemnity of the trial will be provided by the University of Southampton.

**9.6 SPONSOR**

The University of Southampton is acting as the sponsor for this trial. The Chief Investigator has been delegated duties by the Sponsor relating to: submissions to regulatory authorities, GCP and pharmacovigilance. Other delegated duties will be assigned to the GP practices by means of the site clinical trial agreement, if appropriate.

**9.7 DEVIATIONS AND SERIOUS BREACHES**

Any trial protocol deviations/violations and breaches of Good Clinical Practice occurring at sites should be reported to the trial manager and the local R&D Office immediately. The trial manager will then advise of and/or undertake any corrective and preventative actions as required.

All serious protocol deviations/violations and serious breaches of Good Clinical Practice and /or the trial protocol will immediately be reported to the regulatory authorities and other organisations, as required in the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

**9.9 AUDITS AND INSPECTIONS**

The trial may be subject to inspection and audit by University of Southampton, under their remit as sponsor, and other regulatory bodies to ensure adherence to ICH GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

# 10. TRIAL MANAGEMENT

The Trial Management Group (TMG) is responsible for overseeing progress of the trial. The day-to-day management of the trial will be co-ordinated through the trial manager and oversight will be maintained by an independent Trial Steering Committee made up of a primary care trials expert, a PPI representative, a dermatologist and a medical statistician. A separate Data Monitoring and Ethics Committee is not needed for this trial as the trial is not blinded and is very low risk as bath emollients have been used for many years with no safety concerns and they are being used within their licensed range of indications.

# 11. PUBLICATION POLICY

All publications and presentations relating to the trial will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group, if this does not conflict with the journal's policy. If there are named authors, these will include at least the trial's Chief Investigator, Statistician and Trial Manager. Members of the TMG will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy. Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group.

Results will be sent to trial participants using an end of study Newsletter, and will be posted to members of relevant organisations (UK Dermatology Clinical Trials Network, British Society of Paediatric Dermatology, British Dermatology Nursing Group) and on relevant websites (e.g. National Eczema Society; Nottingham Support Group for Carers of Children with Eczema; Centre of Evidence Based Dermatology (CEBD)).

# 12. PLAN OF INVESTIGATION AND TIMETABLE

## 12.1 TIMETABLE

1-6 mths: R&D approvals, publish protocol, prepare study materials & database, set up randomisation. 7-15 mths: internal pilot phase to ensure recruitment and retention is at least 80% expected, followed by trial steering committee meeting at 15 mths to address remediable factors and progression criteria. 16-24 mths: recruitment and follow-up. 19-36 mths: 12mth follow-up. 36-38 mths: data preparation and analysis. 39-42 mths: final reports, dissemination.

| Milestones | Prior to start | 0 to 6 months | 7 to 12 months | 13 to 18 months | 19 to 24 months | 25 to 30 months | 31 to 36 months | 37 to 42 months |
|---|---|---|---|---|---|---|---|---|
| Approval by ethics, MHRA and sponsor | | | | | | | | |
| Appoint staff | | | | | | | | |
| R&D approvals | | | | | | | | |
| Site set-up / training | | | | | | | | |
| Pilot phase | | | | | | | | |
| Review stopping criteria for pilot | | | | | | | | |
| Recruitment | | | | | | | | |
| Follow-up | | | | | | | | |
| Protocol registration | | | | | | | | |
| Publish protocol | | | | | | | | |
| Data cleaning | | | | | | | | |
| Database lock | | | | | | | | |
| Analysis & write-up | | | | | | | | |
| Dissemination & implementation | | | | | | | | |
| Research nurse 21m | | | | | | | | |
| Administrator 21m | | | | | | | | |
| Research assistant 12m | | | | | | | | |

## 12.2 PROJECT MANAGEMENT

The trial will be sponsored by the University of Southampton and run in accordance with the University's standard operating procedures (SOPs). It will be managed through the University of Southampton Primary Care and Populations Science Academic Unit (UoS PCPS) and the University of Southampton Clinical Trials Unit (UoS CTU) in collaboration with the Centre for Academic Primary Care at the University of Bristol, the Institute of Primary Care and Public Health and the South East Wales Trials Unit at Cardiff University and the Centre for Evidence Based Dermatology at Nottingham University. An independent Trial Steering Committee (TSC) will be established on behalf of the NIHR HTA prior to initiation of the trial. This group will oversee the conduct of the trial and ensure patient safety.

The BATHE trial will be a collaboration between a trials unit (UoS CTU) and three regional centres, each with a strong patient recruitment potential and track record backed up by international excellence in research methods and research networks (South West Hub of the Primary Care Research Network in England and National Institute for Social Care and Health Research Clinical Research Collaboration in Wales). Each centre will take responsibility for regional recruitment and trial management within their region. UoS PCPS will lead on developing trial protocol, developing participant information and other study paperwork and obtaining ethical and MHRA approvals, statistical analysis and trial report. UoS CTU will run the randomisation service and lead the database management, data entry and monitoring of data quality. UoS PCPS and UoS CTU will liaise on development of paper and electronic case report forms.

*Trial Steering Committee (TSC):* A TSC will meet at least once a year, consisting of an independent chair, and two/three other independent members. We will ensure that a patient representative and all appropriate disciplines are covered in choosing the TSC members. The first meeting will be before the trial commences to review the protocol and arrange the timelines for the subsequent meetings. The chief investigator, trial manager and statistician will attend as observers. The TSC will provide overall supervision for the trial and provide advice through its independent chair. The ultimate decision for the continuation of the trial lies with the TSC.

*Trial Management Group (TMG)*: The TMG will consist of the co-applicants and collaborators, Trial Manager, Trial Statistician and Trial Administrator. The role of the TMG is to help set up the trial by providing specialist advice, input in and comment on the trial procedures and documents (participant information, protocol etc) and advise on the promotion and the running of the trial. The group will meet every 1 to 2 months during the trial and more frequently at the beginning of the study. This group will also review and advise on the reporting of SAEs. The meetings will be predominantly via audio conference, but with an initial face-to face meeting.

*Internal Project Group:* This Group will consist of the Chief Investigator, Trial Manager and Trial Administrator and will meet weekly to discuss the day-to-day issues that arise from the trial. Important discussions will be relayed to the TMG to for a final decision.

Given the relative safety of bath emollients and their availability to purchase over-the-counter, it is our view that a separate Data Monitoring Committee is not required for this trial.

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